NEURAL CORRELATES AND EFFECTS OF INCREASED COGNITIVE LOAD ON PERFORMANCE DURING THE N-BACK TASK IN MAJOR DEPRESSIVE DISORDER

By

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ABSTRACT

Background: Major depressive disorder (MDD) is a heterogenous disease that includes debilitating cognitive deficits, including working memory (WM). The n-back task used to examine WM as it requires continuous updating and recall. The present study examined the effects of MDD and cognitive load during the n-back task (0- and 2-back). The following were predicted, as cognitive load increased: (1) participants would display decreased accuracy and increased reaction time; (2) increased activity would be found in regions associated with WM; and (3) MDD symptoms and accuracy would be correlated with functional activity in these regions.

Methods: MDD patients (n = 29) completed the n-back task during a functional magnetic resonance imaging scan. Behavioural and imaging data were analysed between conditions. Montgomery-Åsberg Depression Rating Scale (MADRS) scores and task accuracy were correlated with functional activity for each participant.

Results: Compared to 0-back, participants demonstrated decreased accuracy and longer reaction times in the 2-back condition. During the 0-back condition, activity was seen in the bilateral insula and the middle occipital gyrus; in the 2-back condition, activity was seen in the middle and medial frontal gyri and the inferior parietal lobule. MADRS scores were not significantly correlated with activity in either condition. Activity in all regions identified in the 2-back condition were positively correlated with performance accuracy.

Discussion: In the 0-back condition, activated regions are associated with resting state activities and the processing of visual stimuli. Compared to the 0-back condition, higher levels of activity were found during 2-back in the middle and medial frontal gyri and inferior parietal lobule, which are associated with WM, visual processing, and complex cognitive processes, indicating that participants required more neural resources during the more difficult task. Significant and mid-

sized effects were found in the 2-back condition between accuracy and activity in the middle and medial frontal gyri and inferior parietal lobule, suggesting that MDD patients require more effort to perform well in cognitively demanding tasks. Limitations include the small and largely female sample, which would be improved by including more participants and considering covariates.

CO-AUTHORSHIP

Drs. Christopher Bowie and Roumen Milev (Department of Psychology, Centre for Neuroscience Studies, and Department of Psychiatry) are both principal investigators for CAN-BIND 9; this thesis is an interim analysis based on recruited participants for this study. They were both paramount to the overall design and execution of CAN-BIND 9, as well as the funding for this project. Dr. Bowie's clinical psychology graduate students were responsible for the collection of clinical data, including MADRS, CNSVS, and demographic information. Finally, I was responsible for conducting the majority of fMRI data collection (with the assistance of Ashleigh Forsyth and Don O'Brien) and completing all pre-processing and analyses steps.

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Love,

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ABBREVIATIONS

5-HT: Serotonin

ACC: Anterior Cingulate Cortex

BA: Brodmann Area

BDNF: Brain-Derived Neurotrophic Factor

CAN-BIND: Canadian Biomarker Integration Network for Depression

CBT: Cognitive Behavioural Therapy

CNSVS: CNS Vital Signs

CR: Cognitive Remediation

CRH: Corticotrophin Releasing Hormone

DA: Dopamine

DMN: Default Mode Network

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

ECT: Electroconvulsive Therapy

FWE: Family Wise Error

HC: Healthy Controls

HPA: Hypothalamic-Pituitary-Adrenal

MADRS: Montgomery-Åsberg Depression Rating Scale

MDD: Major Depressive Disorder

MINI: Mini International Neuropsychiatric Interview

MNI: Montreal Neurological Institute

MRI: Magnetic Resonance Imaging

fMRI: Functional Magnetic Resonance Imaging

NE: Norepinephrine

PFC: Prefrontal Cortex

RECORD: Remote Cognitive Remediation for Depression

ROI: Region of Interest

rTMS: Repetitive Transcranial Magnetic Stimulation

SNRI: Selective Norepinephrine Reuptake Inhibitor

SSRI: Selective Serotonin Reuptake Inhibitor

WM: Working Memory

CHAPTER 1: INTRODUCTION AND OVERVIEW

1.1 Major depressive disorder

Major depressive disorder (MDD) is a chronic mood disorder that affects millions of Canadians annually (Pearson, Janz, & Ali, 2013). Symptoms are heterogeneous in nature; the criteria for MDD in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) includes the presence of at least five symptoms on a nearly daily basis for at least 2 weeks that are indicative of the disorder, which causes significant impairment or distress, and is a deviation from typical functioning (American Psychiatric Association, 2013). These criteria include: depressed mood, loss of interest or pleasure from activities, significant weight loss or gain, decrease or increase in appetite, insomnia or hypersomnia, restlessness or psychomotor retardation, fatigue or energy loss, feelings of worthlessness, hopelessness, or inappropriate guilt, decreased ability to concentrate, think, or focus, and recurrent thoughts of death or suicide (American Psychiatric Association, 2013).

The economic burden of this disorder is staggering. The Canadian economy spends approximately $32 billion annually on direct and indirect consequences of MDD, including lost wages from time off work and loss of work quality, healthcare (e.g., physician appointments, emergency room and hospital visits, and medication), and disability assistance (Sutherland & Stonebridge, 2016). Moreover, approximately 11% of Canadians over the age of 15 years will experience at least one major depressive episode at least once in their lifetime and that 22% of those diagnosed with MDD will be considered treatment resistant (Pearson et al., 2013). This disease is a large source of burden to society, and it is important that the scientific and medical communities work to decrease its prevalence and work towards a better treatment method.

1.2 Etiology of depression

Due to the widespread prevalence of MDD, millions of dollars of funding have been globally allotted to attempt to determine the etiology of the disease and markers of treatment response (Kupfer, Frank, & Phillips, 2012). While a great deal of uncertainty remains, researchers have found commonalities in patients with MDD, such as genetic, molecular, and neurological components (Harmer, Duman, & Cowen, 2017; Saveanu & Nemeroff, 2012).

1.2.1 Genetic and molecular components

Genetic and molecular components of the etiology of MDD are some of the most highly researched factors for the illness. Some of the most commonly described causes of MDD include neurotransmitter, brain-derived neurotrophic factor (BDNF), and the hypothalamic-pituitary-adrenal (HPA) axis malfunction.

1.2.1.1 Neurotransmitters

The monoamine (e.g., serotonin [5-HT], dopamine [DA], and norepinephrine [NE]) hypothesis has been long considered a plausible explanation for the development of MDD (Boku, Nakagawa, Toda, & Hishimoto, 2018; Meyer et al., 2006). Monoamines are a subset of neurotransmitter that are involved in many functions throughout the brain, depending on what structures they innervate (Jesulola, Micalos, & Baguley, 2018). Since its first description over 50 years ago, this hypothesis has become the primary theory behind the development of MDD (Boku et al., 2018; Willner, Scheel-Krüger, & Belzung, 2013). The monoamine hypothesis suggests that the reason behind the development of depressive symptoms can often be linked to a substantial decrease in monoamines in the synaptic cleft, such as 5-HT, DA, and NE (Boku et al., 2018; Meyer et al., 2006; Willner et al., 2013). This theory has become the framework for the majority of

antidepressants that are on the market, as targeting monoamines has been found to be the most effective method of treatment (Jeon & Kim, 2016).

Studies have found that diminished levels of monoamines have direct implications on functioning, which is explicitly clear in comparison to MDD symptomology. 5-HT is suggested to have projections throughout the entirety of the brain and is imperative in mood, emotion regulation, and many other symptoms that appear in MDD (Jeon & Kim, 2016; Jesulola et al., 2018). Alternatively, DA and NE do not project throughout the brain and are more isolated in their innervation patterns. DA functions primarily as part of the reward circuitry and helps to reinforce behaviours, whereas NE is critical in the sympathetic nervous system and the fight or flight response (Saveanu & Nemeroff, 2012). As a result of their functions, these neurotransmitters are crucial in the maintenance of mental health and can be linked to depressive symptoms. For example, anhedonia, the lack of pleasure, is often thought to result from the substantial lack of DA found in MDD (Saveanu & Nemeroff, 2012).

As described in Chapter 1.3.1, antidepressants (mainly selective serotonin reuptake inhibitors [SSRI] and selective norepinephrine reuptake inhibitors [SNRI]) are the first line of treatment in MDD, which is supported by the large accumulation of research outlining the monoamine hypothesis, as well as the abundance of evidence indicating their efficacy (Kennedy et al., 2016). SSRIs and SNRIs work by blocking the reuptake of 5-HT and NE in the synaptic cleft, therefore retaining the neurotransmitters in the synapse (Caron & Gether, 2016). By doing so, neurotransmitters remain circulating through the brain, which ultimately ends up increasing the serum concentration of 5-HT and NE and improving MDD symptoms (Caron & Gether, 2016; Harmer et al., 2017).

1.2.1.2 Brain-derived neurotropic factor

BDNF is a critical protein found throughout the brain and the human body in the plasma and serum of the blood (Lee, Kim, Park, & Kim, 2007). Its primary function is to promote nerve growth and affects synaptic connectivity and plasticity (Matrisciano et al., 2009). Both preclinical and clinical studies have found that BDNF is significantly and dramatically reduced in MDD patients, particularly prominent in the hippocampus, which is implicated in synaptic plasticity and memory formation (Lee et al., 2007; Molendijk et al., 2014). The exact mechanism behind why BDNF levels are substantially reduced in MDD patients has yet to be fully elucidated; however, some researchers suggest that stress (i.e., illness) causes the downregulation of BDNF in people with MDD, thereby inciting the decrease in neural plasticity and connectivity and failure to promote neuronal growth (Phillips, 2017).

Research has further found that this altered BDNF serum level can be reinstated through repeated administration of antidepressants as well as exercise (Ghosh, Gupta, Bhatia, Tripathi, & Gupta, 2015; Kallies et al., 2019). In studies of MDD patients compared to healthy controls (HC), researchers have found that at baseline, MDD patients have significantly lower serum BDNF levels; however, after administration of antidepressants, BDNF levels increase and are more comparable to those of the HC (Piccinni et al., 2008; Shimizu et al., 2003). It is suggested that antidepressants stimulate the upregulation of BDNF, thereby increasing plasma and serum concentrations, decreasing neural atrophy, and potentially improving cognitive deficits present in MDD (Piccinni et al., 2008). Additionally, researchers have found that repeated exercise boosts BDNF in the periphery, also improving MDD symptoms (Kallies et al., 2019).

1.2.1.3 Hypothalamic-pituitary-adrenal axis

The HPA axis, as the name describes, includes the hypothalamus and the pituitary and adrenal glands, and is in control of glucocorticoid synthesis. Following a negative feedback loop,

stress stimulates the release of corticotropin releasing hormone (CRH) from the hypothalamus, in turn stimulating the pituitary gland to release adrenocorticotropic hormone, which finally stimulates the adrenal gland to secrete cortisol and other glucocorticoids (Aihara et al., 2007; Mehta & Binder, 2012). As cortisol levels increase, this supresses the feedback loop and "shuts off" the release of CRH from the hypothalamus, therefore inhibiting the stress response (Aihara et al., 2007; Mehta & Binder, 2012).

Cortisol is one of the main glucocorticoids secreted through the HPA axis; as a result, its most notable function is to mediate the response to stressful stimuli, but also assists in gluconeogenesis and the immune response (Colman, 2015). Many studies have found significant hypercortisolism in patients with MDD compared to controls, which is induced by dysregulation of the HPA axis (Aihara et al., 2007; Colla et al., 2007; Keller et al., 2017; Salvat-Pujol et al., 2017). It is suggested that, for unknown reasons, the HPA axis feedback loop is affected in MDD patients, thereby allowing the massive over secretion and serum levels of cortisol (Eikeseth et al., 2019). The large abundance of cortisol in MDD is thought to lead to some of the symptoms experienced by patients such as the cognitive and sleep deficits (Keller et al., 2017). The hippocampus has a high volume of mineralocorticoid receptors that bind cortisol, which leads to extensive hippocampal atrophy, thereby affecting memory and emotion regulation (Keller et al., 2017; Milne, MacQueen, & Hall, 2012; Vythilingam et al., 2004). Additionally, as cortisol is one of the main regulators of the circadian rhythm, an increased level of cortisol can blunt the circadian rhythm, inducing the sleep disturbances largely reported in MDD patients (Keller et al., 2017).

By reducing MDD symptoms through pharmacotherapy, this can decrease stress, therefore normalizing HPA axis dysfunction and decreasing serum cortisol to a healthier level (Aihara et al., 2007; Salvat-Pujol et al., 2017).

1.2.2 Neurological

Several substantial neurological differences have been demonstrated in MDD patients; however, it is unclear if they are risk factors of the illness or are a result of it. Profound structural and functional differences have been cited in MDD patients when compared to HC, which can be seen as early as the first major depressive episode. Anomalies are also often more severe as symptoms become more profound or longer lasting (Canu et al., 2015). Additionally, some of the most intense alterations, both structural and functional, can be seen in areas of the brain that are imperative in emotion regulation and cognition (Kupfer et al., 2012).

1.2.2.1 Structural differences

Structurally, the largest areas that exhibit these differences are the hippocampus, prefrontal cortex (PFC), and amygdala (Liu et al., 2017; Saveanu & Nemeroff, 2012). Some regions, as a result of the illness, demonstrate significant atrophy, while others display hypertrophy; these may vary based on hormones and neurotransmitters that innervate them or their primary function.

The hippocampus is a fairly small structure found in the medial portion of the temporal lobe whose primary roles are in long-term memory formation, emotion regulation, and motivation (Colman, 2015). Studies have found that MDD patients exhibit significant hippocampal atrophy, which can largely be attributed to the excess cortisol and decreased BDNF (see Chapters 1.2.1.2 and 1.2.1.3) (Liu et al., 2017). The repeated exposure to stress causes the atrophy of dendrites, therefore inciting substantial volumetric changes throughout the hippocampus, which may aid in the memory symptoms found in MDD (Willner et al., 2013). Moreover, these changes are present in patients who have only experienced one episode of MDD, inferring that this atrophy may be a neurological biomarker for the development of the disease (Cole, Costafreda, McGuffin, & Fu, 2011). Overall, there have been many studies examining the impact of MDD on the hippocampus,

and have found significant atrophy as part of the illness, indicating a potential risk factor, or offering a deeper understanding into the etiology of the disease (Amico et al., 2011; Frodl et al., 2002; Janssen et al., 2004; Kempton et al., 2011). Importantly, there has been evidence that this hippocampal atrophy can be reversed after depressive symptoms have subsided but can also be facilitated through the use of antidepressants and exercise. As discussed in Chapters 1.2.1.2 and 1.2.1.3, BDNF and cortisol are two important for the effective structure and function of the brain. As BDNF is seen to be downregulated and cortisol is seen in excess in MDD, the function of these two factors exert their effects on the hippocampus and can lead to significant atrophy, since they can be neurotoxic at unregulated levels (Ghosh et al., 2015; Kallies et al., 2019; Keller et al., 2017). Through the elimination of MDD symptoms through antidepressants and exercise, which decrease cortisol and increase BDNF, hippocampal neurogenesis may resume and help to aberrate some of the cognitive symptoms (Sahay & Hen, 2007).

The PFC is another structure in the brain that has been found to be extremely affected, both structurally and functionally, in MDD. The PFC is a region at the forefront of the brain and has a wide variety of functions, including working memory (WM), executive functioning, and self-awareness (Colman, 2015). In MDD, there are substantially more functional differences noted; however, structural differences have been cited as well. MDD has been found to be correlated with lesions in the dorsolateral PFC, and volume loss in the right ventromedial PFC associated with early life stress (Liu et al., 2017). It is suggested that, like the hippocampus, the neuronal atrophy may be due to the neurotoxic effects of stress; therefore, this may be remedied through pharmacotherapy and psychotherapy (Liu et al., 2017; Ramkumar et al., 2012).

Finally, the amygdala has been found to display atrophy in patients with MDD. The amygdala is a structure found to be critical in the processing of emotion and fear, and is also

imperative in anxiety and stress responses (Vyas, Pillai, & Chattarji, 2004). In preclinical studies, the repeated administration of stress and cortisol have been noted to induce neuronal growth in the amygdala, thereby leading to its hypertrophy (Lakshminarasimhan & Chattarji, 2012; Mitra & Sapolsky, 2008; Vyas et al., 2004; Willner et al., 2013). Conversely, while hippocampal atrophy appears to worsen as the course of MDD progresses, studies have found that alterations in the amygdala remain stagnant following the first episode (Willner et al., 2013). However, these findings remain somewhat controversial and require more study to confirm their accuracy.

1.2.2.2 Functional differences

Impairments in function are more robustly demonstrated in clinical MDD populations and are most often seen in the anterior cingulate cortex (ACC), PFC, and amygdala, which are all critical in the regulation of affect (Connolly et al., 2013).

The ACC is a structure found in the frontal regions of the brain that is imperative in several facets of cognition and emotion, and is especially critical in the processing of emotional stimuli (Jaworska, Blier, Fusee, & Knott, 2012). In studies of patients with MDD, significantly increased activity has been found during cognitive tasks of executive functioning, and is significantly correlated with severity and duration of illness (Mirza et al., 2004; Wagner et al., 2008). It is suggested that during these types of tasks, MDD patients are unable to separate the emotions from the task as effectively as HC; therefore, the ACC must work harder in order to achieve the same performance (Wagner et al., 2008). Furthermore, hyperactivity is seen in the ACC when patients with MDD are exposed to negative self-descriptive words, indicating once again there may be an overexaggerated response in this region to negatively valanced emotions (Quevedo, Doty, Roos, & Anker, 2017).

Next, the PFC is also noted to have significant alterations in function in MDD. The PFC is broken into several sections, depending on their location in the brain and they demonstrate differences in activity during cognitively demanding tasks. Overactivity is found in the ventromedial PFC while MDD is active; the ventromedial PFC is indicated to be especially involved in the generation and processing of negative emotions (Liu et al., 2017). Therefore, as MDD induces negative emotions and thoughts, it is understandable that participants would demonstrate a much higher activity in this region than HC. Overall, the PFC has many functions and responsibilities, and as a result it appears to be largely affected in MDD.

The amygdala, as earlier described, is a region of the brain that is also largely implicated in emotions, namely fear. Therefore, participants with MDD have been found to demonstrate a significant amount of hyperactivity in this region during emotionally charged tasks involving negative emotions or fearful stimuli (Liu et al., 2017). Furthermore, it is suggested that aberrant functioning in this region may be a risk factor for MDD, demonstrating that this group may be predisposed to using more cognitive resources on negative events (Liu et al., 2017).

1.3 Treatment of depression

As MDD is a complex disorder, it is difficult to treat, occasionally leading to treatment resistance, largely due to its symptom heterogeneity and disparity in etiology. There are many effective forms of treatment, ranging from pharmacological interventions (i.e., antidepressants) to more intense and invasive interventions, such as electroconvulsive therapy (ECT).

1.3.1 Antidepressants

Pharmacological intervention remains the first-line treatment for MDD, with SSRIs and SNRIs being the most commonly prescribed antidepressants (Harmer et al., 2017; Kennedy et al., 2016). These drugs act primarily on the serotonin and norepinephrine receptors throughout the

brain to increase the synaptic concentration of the neurotransmitters by preventing them from re-entering neurons through the inhibition of monoamine transporters (Harmer et al., 2017; Jeon & Kim, 2016). As described in Chapter 1.2.1.1, by preventing this, neurotransmitters are retained in the synapse, therefore allowing their circulation throughout the brain and body (Caron & Gether, 2016). There are other classes of antidepressants that are available, such as monoamine oxidase inhibitors and tricyclic agents; however, SSRIs and SNRIs remain the most effective in the majority of patients (Kennedy et al., 2016).

While the full benefits of SSRIs and SNRIs take several weeks to take effect, they remain the first-line treatment due to their efficacy in reducing depressive symptoms and tolerability (Harmer et al., 2017; Kennedy et al., 2016). Moreover, large meta-analyses have found that approximately 50-60% of patients respond favourably to antidepressant treatments (Arroll et al., 2005; Cleare et al., 2015). Despite their obvious advantages in improving quality of life in depressed individuals, antidepressants can have intolerable adverse effects and only have an approximately 28% attrition rate after 3 months of treatment (Olfson, Marcus, Tedeschi, & Wan, 2006). Frequently cited adverse effects of commonly used SSRIs and SNRIs include daytime sleepiness, dry mouth, sexual dysfunction, profuse sweating, and weight gain (Bet, Hugtenburg, Penninx, & Hoogendijk, 2013). These adverse effects are often deterrents to continuing treatment, as they can range in severity from mild (hardly noticeable) to severe (incredibly bothersome; (Bet et al., 2013; Kennedy et al., 2016).

Antidepressants provide a large improvement in depressive mood symptoms, but they also offer benefits for other symptoms, including memory loss and concentration. As described in Chapters 1.2.1.2 and 1.2.1.3, BDNF and cortisol are two major contributors to healthy and effective neural function and have detrimental effects when faulty. Through the introduction of

antidepressants, these deficits can be controlled and reversed by boosting BDNF activity and decreasing cortisol through the removal of stress (Aihara et al., 2007; Ghosh et al., 2015; Kallies et al., 2019; Keller et al., 2017; Salvat-Pujol et al., 2017).

1.3.2 Psychotherapy

As previously described, MDD can be the result of various sources, including environmental experiences and personality traits. Therefore, psychotherapeutic interventions are often recommended, often in conjunction with pharmacotherapeutic treatments (Kennedy et al., 2016). There are several types of therapies that can be used to treat MDD (i.e., cognitive behavioural therapy [CBT], interpersonal therapy, and nondirective supportive therapy); however, they are all found to be equally effective with differences lying in variation in the relationship between the therapist and patient and whether the patient believes the treatment will be helpful (Cuijpers, van Straten, Andersson, & van Oppen, 2008).

Cognitive behavioural therapy (CBT) is one of the most widely used psychotherapeutic treatments in MDD and other mental health disorders; however, despite this, it has not been found to be more effective than other psychotherapies (Baardseth et al., 2013; Chawathey & Ford, 2016; Cuijpers et al., 2008). CBT is a structured talk therapy that works to change and redirect maladaptive and dysfunctional thought processes (Chawathey & Ford, 2016; Cuijpers et al., 2008). Patients with MDD often find CBT to be effective in modulating their depressive symptoms, especially in distorted thoughts and thought processes, with this advantage mirrored in clinical data (Lepping et al., 2017).

Treatment regimens including both pharmacotherapy and psychotherapy have become increasingly common in a large portion of MDD patients, as illness development is often a combination of many different factors that lead to the perverse symptoms experienced, as earlier

described. Patients who utilize this combination therapy typically have better success in achieving remission than patients who select only one (Kamenov, Twomey, Cabello, Prina, & Ayuso-Mateos, 2017).

1.3.3 Cognitive remediation

CR is an intervention that works to improve the cognitive deficits that are commonly seen in neurocognitive disorders and cannot typically be improved through pharmaco- or psychotherapy, including attention, memory, executive function, wand social function (Bowie et al., 2013; Galletly & Rigby, 2013; McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Trapp, Engel, Hajak, Lautenbacher, & Gallhofer, 2016; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011). It is a relatively new therapy (i.e., within the last approximately 20 years) that was first implicated in the functional treatment of schizophrenia and has since been determined to be a highly effective therapy in the functional recovery of the disorder; moreover, CR has been utilized in MDD and other disorders with, such as bipolar disorder and anorexia nervosa, with demonstrated efficacy (Bowie et al., 2013; Bowie, McGurk, Mausbach, Patterson, & Harvey, 2012; Lock et al., 2013; Meusel, Hall, Fougere, McKinnon, & MacQueen, 2013; Naismith, Redoblado-Hodge, Lewis, Scott, & Hickie, 2010; Trapp et al., 2016).

To continue, CR is an intervention that works to improve many aspects of cognition through behavioural training exercises (Wykes et al., 2011). Researchers suggest that by improving the cognitive deficits that are present in neurocognitive disorders, such as schizophrenia and MDD, that this will in turn aid in improving function within the community (Wykes et al., 2011). One of the appealing aspects of CR is that while it can be administered either directly through a clinician or through a computer with clinician supervision; however, computerized CR is preferable as less staff are required to administer the intervention and is generally easier to run (Galletly & Rigby,

2013). In computerized CR, patients engage in brief games/tasks that are designed to target the various facets of cognition; overall, this training helps to improve these domains (Galletly & Rigby, 2013).

It is suggested that CR is effective in improving functional outcomes of illnesses because it targets (both structurally and functionally) neuroplastic regions of the brain that are implicated in these disorders, including the PFC, insula, hippocampus, and amygdala (Eack et al., 2010; Ramsay & MacDonald, 2015). While neuroimaging studies on the efficacy of CR remain scarce, other studies have suggested through their clinical results that neuroplasticity may be improved through the use of this intervention as patients have demonstrated a restoration of function through treatment (Naismith et al., 2010).

While research outlining the efficacy of CR in MDD is sparse, it reaches the same conclusion that it may be an effective adjunct treatment for functional recovery in this population (Bowie et al., 2013; Kim et al., 2018; Meusel et al., 2013; Naismith et al., 2010). However, to completely understand the use of CR in the MDD population, more studies are required.

1.3.4 Other treatments

Despite many treatments that are readily available, there are patients that remain resistant to these and require alternative therapies. These are often treatments that are considered extreme and at times invasive but demonstrate their efficacy in treatment resistant patients. Alternative treatments include ECT and repetitive transcranial magnetic stimulation (rTMS).

1.4 Working memory

Cognition encompasses numerous processes that are utilized to interpret incoming information and stimuli, such as attention, memory, executive functioning (e.g., the ability to plan and complete tasks), and focus. Cognitive impairments, particularly in memory, are common in

MDD and as earlier described are one of the diagnostic criteria of the illness. Many patients with MDD endorse profound memory impairments, which is seen in self-reported and clinical data.

Specifically, many MDD patients express difficulties in WM, which is the active process by which the brain gathers information and temporarily stores it to manipulate various tasks and situations (Blacker, Negoita, Ewen, & Courtney, 2017; Li et al., 2018; Owen, McMillan, Laird, & Bullmore, 2005; Rottschy et al., 2012; Yüksel et al., 2018). Many illnesses have been found to affect WM, especially those that have neurological etiologies, including Parkinson's, Alzheimer's, and Huntington's diseases, multiple sclerosis, and psychiatric disorders such as MDD and schizophrenia (Georgiou-Karistianis et al., 2014; Grogan et al., 2018; Keshavan et al., 2011; Kirova, Bays, & Lagalwar, 2015; Kollndorfer et al., 2013; Li et al., 2018). There are many illnesses that can negatively impact WM; this may be due to lesions, neural atrophy, or functional differences that are present (Blokland et al., 2017). Additionally, as age increases, there are often WM deficits along with other cognitive impairments, which are often associated with increased neural activity in regions implicated in WM (see Chapter 1.4.1; Dumas et al., 2013).

WM has several components and steps that are critical to its proper functioning; if one of these processes is not working effectively, it can create deficits in WM. Initially, WM can be broken into two primary functions: storage (i.e., maintenance) and processing (i.e., updating and manipulation of information; Ecker, Lewandowsky, Oberauer, & Chee, 2010; Rac-Lubashevsky & Kessler, 2016). As information enters the brain, regions associated with WM are working continuously to store, update, manipulate, and process the information to be used at a later point in time (Cowan, 2014).

One interesting facet of WM is that training programs exist that work to improve all aspects of WM in participants with varying diagnoses or severities in function. Cognitive training

programs work to improve cognition, with WM as one of the targeted domains (Soveri, Antfolk, Karlsson, Salo, & Laine, 2017). Those who engage in WM training often participate in brief game-like tasks that work to improve the storage and manipulation of the stimuli, thereby increasing cognitive load and recall time that is often transferred to everyday situations (Soveri et al., 2017).

1.4.1 Neural correlates of working memory

As WM is a complex process, there are several regions of the brain that have been implicated in its effective functioning. A large meta-analysis of 189 functional magnetic resonance imaging (fMRI) studies in healthy participants determined the most common areas involved in WM tasks were the premotor cortex, PFC, anterior insula, supplementary motor area, and Brodmann's area (BA) 44/45 (Rottschy et al., 2012). The areas that are primarily activated did differ based on the WM task; however, the previously mentioned regions are those that are most consistently activated across differing task types (i.e., visual versus auditory versus object identification; Rottschy et al., 2012).

As earlier described, the PFC is a region of the brain that is implicated in cognition, including WM, making it one of the primary regions assessed in deficits of WM. The premotor cortex, as its name suggests, is largely involved in movement, especially during the examination of visual and tactile stimuli (Colman, 2015). Many WM tasks are visually inputted and require the use of buttons, thereby offering understanding to this finding. Next, the anterior insula is largely involved in self-reflection and emotion, which may be activated as a result of thought during WM task engagement or as a result of an emotionally valanced task (Smith et al., 2017). The supplementary motor area is important in the planning and execution of behaviours; therefore, its activation and significance in WM tasks is unsurprising (Alario, Chainay, Lehericy, & Cohen, 2006). Finally, BA 44/45 makes up Broca's area, which is activated in tasks involving speech and

language; many WM tasks involve the reading of words or listening to a list, thereby offering explanation to the significant activation of this region as well (Amunts et al., 2004).

1.4.2 Working memory in depression

Notably, MDD patients have been found to display significantly affected WM in cognitively demanding tasks when compared to HC (Doumas, Smolders, Brunfaut, Bouckaert, & Krampe, 2012). Other studies have corroborated this; using several assessments of WM (e.g., Sternberg, n-back, verbal task), MDD consistently perform worse than HC across tasks using varying input modalities (Li et al., 2018; Rose & Ebmeier, 2006; Vasic, Walter, Sambataro, & Wolf, 2009).

It has been described that patients with MDD may demonstrate such profound difficulties in WM as it is more cognitively taxing on resources to perform these tasks as well as HC (Bowie, Milanovic, Tran, & Cassidy, 2017). Other than that these regions are already overworked with other thoughts, it is suggested that MDD patients perform so poorly due to little self-belief they can achieve optimal results, which often leads to patients "giving up" (Bowie et al., 2017).

1.5 N-back task

The n-back task was first described in 1958 by Kirchner as a task used to assess WM in human participants (Kirchner, 1958). The task can be conducted in several settings, including both in an fMRI and outside of it. In the n-back task, 'n' represents a predetermined number (typically between 0 and 3), and the participant is required to designate whether the image/stimulus presented matches that of 'n' trials prior (Owen et al., 2005). In a 0-back trial, which is often considered a control trial, rather than matching the stimuli to that of 'n' trials prior, they are given a target stimuli and are asked if the stimulus presented matches that target (Wang et al., 2019). Additionally, as 'n' increases, the task becomes arguably more difficult, as cognitive load is

exponentially increased (León-Domínguez, Martín-Rodríguez, & León-Carrión, 2015; Owen et al., 2005; Wang et al., 2019).

The n-back task is often used in studies of WM as it targets several aspects of WM, including decision making (i.e., does the current stimulus match the target?), storage, retrieval, updating, and maintenance (Jiang et al., 2015; Rac-Lubashevsky & Kessler, 2016; Zhang, Xie, He, Wei, & Gu, 2018). The n-back task not only employs these aspects of WM, but it requires their constant and continuous use in conjunction with one another to achieve the highest possible accuracy (Rac-Lubashevsky & Kessler, 2016). Notably, the n-back task does not typically use emotionally stimulating items (i.e., it uses those that are neutral, such as a hammer, a word [e.g., candle, bed, stairs], or a number), which ensures that neural networks involved in emotional processing are not employed (Zhang et al., 2018).

1.5.1 Neural correlates of the n-back task

A meta-analysis of 24 studies found that the neural correlates associated with the n-back task found that the regions with the largest amount of activation during the task are the lateral premotor cortex, dorsal cingulate cortex, medial premotor cortex, dorsolateral and ventrolateral PFC, frontal poles, and medial and lateral posterior parietal cortex (Owen et al., 2005). While the studies used primarily healthy participants (i.e., no physical or mental illnesses), a variety of stimuli (i.e., letters, faces, auditory tones, shapes, etc.), and differing conditions (i.e., 0-back, 1-back, 2-back, and 3-back), these results were still seen in all studies as significant regions of activity (Owen et al., 2005).

Additionally, due to the differences in stimuli, the n-back task can demonstrate differences in regions of activity. For example, if the task is verbally assessed, regions such as Broca's area

are found to be active, whereas in tasks requiring the physical manipulation of objects, activity is found in the ventral and dorsal PFC (Rottschy et al., 2012).

1.5.2 Changes in cognitive load

Cognitive load refers to the amount of neural resources required to complete a task (Sweller, 2011). The cognitive load of a task is determined by the amount of time spent allocating these resources to the task, rather than to other inputs that may require attention (Barrouillet, Bernardin, Portrat, Vergauwe, & Camos, 2007). WM tasks that are more cognitively demanding, in that there is more information that needs to be stored at a time, require more attention, which typically demonstrates an increase in activity. Studies have found that structures in the fronto-parietal region of the brain, including the PFC, are affected as a result of changing cognitive loads throughout WM tasks (Diwadkar et al., 2011). Additionally, in the literature, it has been cited that as cognitive load increases, participants demonstrate longer reaction times and decreased accuracy; it is unquestionably more difficult to perform well on a task when there is more information that needs to be stored, updated, and recalled at any given time (Bartova et al., 2015; Vatansever, Manktelow, Sahakian, Menon, & Stamatakis, 2017). The use of the n-back task can assess two aspects of WM: its capacity and function (Karbach & Verhaeghen, 2014). By adjusting 'n' and increasing/decreasing the cognitive load participants must take on, this can assess both its capacity and its function at differing loads (Karbach & Verhaeghen, 2014; Vatansever et al., 2017).

Additionally, as 'n' and therefore cognitive load increases and the task becomes more difficult, studies of HC have found differences in neural activity. In a verbal n-back task, León-Domínguez and colleagues (2015) found that as the task difficulty increased from 0-back to 2-back, participants showed greater activation in the dorsolateral PFC and left frontal opercula. These regions are indicated to be involved in executive functioning, thus suggesting that as the

task became more difficult, their participants required more control over their behaviour and thought processes than during the 0-back condition (León-Domínguez et al., 2015).

1.5.3 N-back performance in depression

Since there is an evident disparity in WM capabilities between HC and MDD patients, it can be inferred that a similar trend would be seen during the n-back task. Studies have corroborated this; studies have found that MDD patients display significantly increased activity in regions of the brain found to be activated in the n-back task (e.g., the PFC, ACC, and parietal cortex), compared to HC (Harvey et al., 2005; Vasic et al., 2009). This suggests that in MDD patients, participation in the n-back task requires more cognitive resources to complete than in HC. Furthermore, similar to general assessments of WM, patients with MDD have been found to demonstrate significantly worse performance than HC on the n-back task, especially as 'n' increases beyond 0-back (Rose & Ebmeier, 2006).

Interestingly, in patients that have remitted MDD, it has been found that their performance is normalized and does not significantly differ from that of HC, indicating the possibility of recovered WM with treatment and remission (Bartova et al., 2015).

1.6 The present study

The present study was conducted as an interim analysis for the Remote Cognitive Remediation for Depression (RECORD) or Canadian Biomarker Integration Network for Depression (CAN-BIND) 9. RECORD/CAN-BIND 9 is determining the feasibility of remote CR, rather than in person, in a depressed sample. This is significant because, as described in Chapter 1.3.3, CR is typically administered face to face; however, if its remote counterpart is as effective, this may be a useful alternative for patients who are significantly impaired.

This interim analysis will be assessing the functional activity changes that are present in this sample of MDD patients during the n-back task, which will hopefully aid in further understanding some of the neurological underpinnings of WM in moderate to severe MDD. The present study will be assessing the impact of increased cognitive load in MDD, as the n-back task used has both 0-back and 2-back conditions, which will continue to explain the effect of cognitive load in MDD patients. Moreover, using clinical assessments, specifically the Montgomery-Åsberg Depression Rating Scale (MADRS), symptom severity will be correlated with performance on the n-back and activity to determine if there are any significant relationships between illness severity and increased cognitive load.

1.7 Hypotheses

The following are hypothesized, in that as cognitive load increases from 0-back to 2-back, participants will demonstrate:

(1) A decrease in accuracy and increase in reaction time.

(2) An increase in functional activity in areas associated with WM, such as the PFC.

(3) A significant relationship between functional activity in the regions identified in the second hypothesis and MADRS and accuracy scores between the two different conditions.

CHAPTER 2: METHODOLOGY

2.1 Participants

Participants were recruited from various sources (e.g., Providence Care Hospital, Mood Research Lab, within the community) in Kingston, Ontario from August 2017 and with recruitment still active. To be included in the study, participants were required to have a primary diagnosis of MDD, as determined by the Mini International Neuropsychiatric Interview (MINI), have active symptoms at their initial screening (over 20 points on the MADRS, indicating moderate to severe depression), be between the ages of 18-60, and be able to understand English at a minimum of a grade 6 level.

Participants were excluded if they had a current or past diagnosis or history of psychosis, current diagnosis of bipolar I or II disorder (as determined by the MINI), active substance abuse (or within 3 months of screening), ECT within 6 months of screening, any central nervous system condition that would impair their ability to engage in the intervention (e.g., stroke or epilepsy), active suicidal ideation (endorsed by a rating of 4 or higher on the suicidality item of the MADRS), mild cognitive impairment, or any sensory or perceptual conditions that would affect the validity of the results or their ability to engage in the intervention. Additionally, to take part in the imaging component of the study, participants had to ensure they had no nonremovable metal in or on the body, as this could distort the image or cause injury to the participant.

All participants were required to sign an informed consent form outlining the possibility of not receiving true CR treatment and were debriefed following the study period. Before the MRI, participants needed to sign an additional form detailing any medical concerns and ensuring they had no metal objects embedded in their body. The present study was approved by the Queen's University Health Sciences Research Ethics Board.

2.2 Procedure

After meeting inclusion criteria, participants were randomized into one of three groups (1:1:1): 12 weeks of CR (short-term) with treatment discontinuation, 24 weeks of CR, or 12 weeks of sham treatment as an active control group.

At their baseline assessment, participants met with staff to have a battery of clinical assessments conducted to assess functioning, symptoms, and cognition, followed by an fMRI and blood draw for the study of biological markers (genomics and proteomics). This group of assessments was reconducted at weeks 12 and 24, and in the interim, participants in the long-term group received weekly phone calls from staff to ensure compliance. Participants were financially compensated for each visit.

Notably, patients were required to have active symptoms when they were screened, as demonstrated by a MADRS score over 20; however, it was not uncommon for some participants to have improved symptomology by their baseline/first visit, thus demonstrating a much lower MADRS score.

2.3 Clinical assessments

While a large number of questionnaires are used at each visit of CAN-BIND 9, only MADRS and CNS Vital Signs (CNSVS) were used to assess clinical characteristics of participants in the present study.

2.3.1 Montgomery-Åsberg Depression Rating Scale

The MADRS was first created in 1979 by Drs. Montgomery and Åsberg as a more sensitive tool to assess depressive symptoms, rather than using the Hamilton Depression Rating Scale (Montgomery & Asberg, 1979). The MADRS is a clinician-rated, 10-item, Likert scale from 0-6, with 0 indicating no symptoms and 6 indicating the most severe symptoms with limited

functioning; however, each question is scored at degrees of 0, 2, 4, and 6, as these are the prompts that are provided for each question (Bech, Allerup, Larsen, Csillag, & Licht, 2014). Once each question has been answered, the clinician is required to combine each answer to get a total score; higher total scores are indicative of more severe symptoms (Müller-Thomsen, Arlt, Mann, Mass, & Ganzer, 2005). Cut-off scores are debated; however, a score of 20 is typically considered to be indicative of moderate MDD symptoms (Leucht et al., 2017).

As described, the MADRS consists of 10 questions, with each question assessing a different domain of the illness, including: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude (difficulty starting everyday tasks), inability to feel, pessimistic thoughts, and suicidal thoughts (Montgomery & Asberg, 1979). These domains are all part of the DSM-5 criteria of MDD, making this scale an excellent tool for assessing the presence and severity of symptoms.

2.3.2 CNS Vital Signs

CNSVS is a series of computerized tests used in both healthy and clinical participants as a screening tool for neurocognitive deficits (Gualtieri & Johnson, 2006). This battery consists of seven well validated assessments (e.g., visual and verbal memory, finger tapping, symbol digit coding, Stroop task, shifting attention test, and the continuous performance task) that measure different domains of cognition, such as memory, attention, executive function, and motor speed (Gualtieri & Johnson, 2006).

2.4 fMRI data acquisition

All MR images were collected using a 3T (TrioTrim; Siemens, Munich, Germany) scanner with a 12-channel coil at Queen's University. Each scan ran for approximately 45 minutes with several different techniques used. First, there was a whole brain, sagittal, T1-weighted anatomical

scan that lasted for approximately 4.5 mins (repetition time [TR] = 1760 ms, echo time [TE] = 2.2 ms, slice thickness = 1.0 mm, field of view [FoV] = 256 mm, matrix size = 256 × 256, inversion time = 950 ms, number of slices = 192, voxel size = 1.0 × 1.0 × 1.0 mm, GRAPPA = 2). Next, a whole brain T2-weighted blood-oxygen dependent level (BOLD) echo-planar imaging (EPI) series resting state scan (10 mins; TR = 2000 ms, TE = 30 ms, slice thickness = 4.0 mm, flip angle = 75º, FoV = 256 mm, matrix size = 96 × 96, number of slices = 300, voxel size = 4.0 × 4.0 × 4.0 mm, GRAPPA = 2, bandwidth = 2232 Hz/Px). For functional data, an additional whole brain T2*-BOLD EPI series was conducted that lasted roughly 5 mins (TR = 2000 ms, TE = 30 ms, slice thickness = 4.0 mm, flip angle = 75º, FoV = 256 mm, matrix size = 64 × 64, number of slices = 150, voxel size = 4.0 × 4.0 × 4.0 mm, GRAPPA = 2, bandwidth = 2232 Hz/Px). Finally, a whole brain diffusion tensor image scan was administered, lasting approximately 10 mins (TR = 8000 ms, TE = 94 ms, slice thickness = 2.5 mm, FoV = 240 mm, matrix size = 96 × 96 mm, GRAPPA = 2, bandwidth = 1408 Hz/Px, 30 diffusion directions, b-value = 1000 s/mm^2). While in the scanner, participants had their pulse and breathing measured, as well as were given a four-button response pad (HHSC-1X4-L; Current Designs Inc., Pittsburgh, PA, USA) for the functional tasks.

Before participants were put into the scanner, instructions were given for each scan and the tasks were explained in detail with an option to practice beforehand. Additionally, before each scan began, instructions were reiterated to participants through a speaker projecting to the MRI.

2.4.1 fMRI tasks

All fMRI tasks were run using E-Prime version 2.0 software (Psychology Software Tools, Sharpsburg, PA, USA). In addition to the n-back task, a go/no-go task was used to assess affect using emotionally valanced faces (e.g., ‘happy’, ‘sad’, or ‘angry’).

2.4.1.1 N-back

In this study, 0- and 2-back visual conditions were used following a block design. Participants are required to indicate either ‘match’ or ‘no match’ by pressing the button aligned with their either their index or middle finger, respectively. Stimuli included 2D, coloured images of body parts, faces, tools, and landscapes (“places”).

In the 0-back condition, participants are shown a target image and are asked to determine whether the subsequent images shown match that of the target. In the 2-back condition, participants are shown a series of images, in which they need to specify whether the image on the screen matches that of two images prior. During the scan, each condition was presented in four blocks, with 10 stimuli per block (total: eight blocks consisting of 80 trials total). Each block ran for a total of 28 s, with four 15 s fixation crosses after every two blocks. Each stimulus was presented for 2500 ms, with the next image appearing immediately after (i.e., no delay or mask) for the same duration. There was a total of 3 s that was allotted to the beginning of each block that dictated to participants what condition will be presented. For each participant, the n-back task followed the same procedure, as seen in Figure 1.

Notably, participants are required to respond to every image by pressing either their index or middle finger. During scans, if a participant appeared to not be answering for every trial, the scan was stopped, and instructions were reiterated before the scan was restarted. It was not uncommon for participants to forget or get confused while waiting for the task to begin; therefore, responses were monitored for the first block to ensure participants were answering for every image presented to eliminate the possibility of null data.

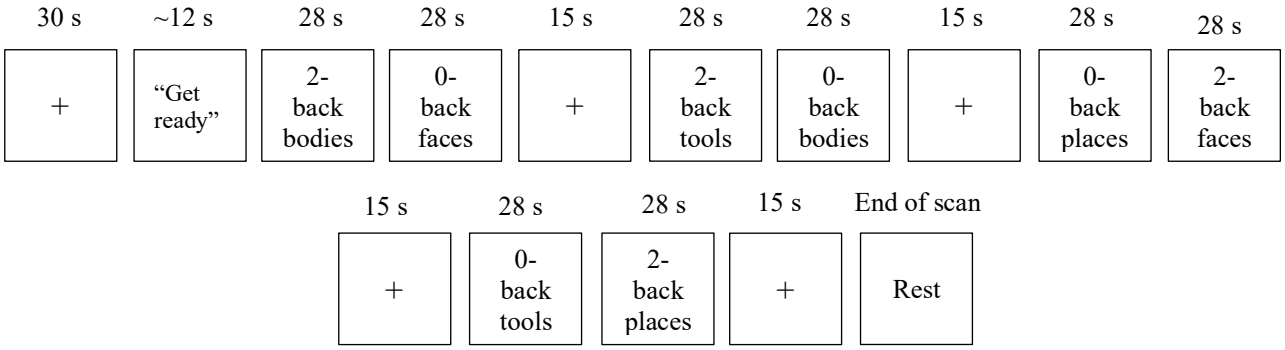

Figure 1. N-back protocol for each participant. This depicts the n-back protocol, which includes fixation crosses (+), written commands to participants ("Get ready"), condition block order along with the stimulus presented, and rest following condition blocks. The duration of each block is listed above each square. Each participant completed this protocol once per scan.

2.5 Pre-processing

All images were pre-processed using SPM12 software (Wellcome Trust Centre for Neuroimaging, London, UK) in MATLAB (MathWorks, Natick, MA, USA). First, all images (total 150 volumes) were converted from the DICOM images the MRI creates to a NIFTI file that SPM12 can utilize. Volumes were motion corrected to remove any motion artefacts from small movements within the scanner, such as breathing, involuntary twitching, or task dependent movements. Next, images were slice timed to ensure that and then co-registered to be compared to their anatomical image to ensure they were in the correct position. All images were then normalized to a Montreal Neurological Institute (MNI) template to provide a basis for make generalizations and conclusions about all participants. Finally, images were smoothed with an 8 mm full-width at half-maximum Gaussian kernel to help increase signal to noise ratio, thereby clarifying conclusions about the data.

2.6 Imaging analysis

Notably, the following functional imaging analysis was conducted on the single run of the n-back task that involved eight total blocks (i.e., four blocks for each condition; 10 trials per block; 80 total trials).

Functional images from the n-back task were first analyzed at a single subject (first) level using SPM12 in MatLab with a high-pass filter of 128 s. Task timings ("Cue2Back.OnsetTime" for 2-back or "CueTarget.OnsetTime" for 0-back) were collected from the E-Prime output files and inputted into the batch editor after some minor manipulations (subtracting first row of "SyncSlide.OnsetTime" column, as this is the onset of the first TR based on the E-Prime clock) to ensure correct timings were inputted. Conditions were created for the 0-back condition, 2-back condition, and the fixation cross periods by including onsets for the beginning of each block and

their duration from the E-Prime files. As this task followed a block design, each condition block could be inputted as having a duration of 28 seconds. Fixation crosses were 15 s in duration, as previously described, but was also modelled for the first approximately 40 s of the scan. Contrasts were created to compare activation in the 0-back and 2-back conditions independent of one another (i.e., 0-back > 2-back; 2-back > 0-back) for each individual participant. Contrasts were run unmasked and uncorrected (i.e., $p < .01$). From here, group (second) level analyses were conducted to determine activity changes between the conditions in the entire sample.

First, all contrast images obtained from the first level analyses were re-smoothed to account for the differences in structure between the participants, thus making it easier to see significant functional activity. Using a one sample t-test, contrast images were selected and run for each contrast specified in the first level analysis. Contrasts were then created for each t-test and were run unmasked and corrected with a family wise error (FWE) of $p < .05$. In the 0-back condition, there were many small and non-significant clusters found, so the extent voxel threshold was set to 10 voxels. In the 2-back condition, there were far fewer clusters, so there was no extent voxel threshold specified (i.e., threshold was 0). MNI coordinates (x, y, z) from significant voxel clusters were obtained directly from SPM12 output, recorded, and transformed into Talairach coordinates (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). Next, the Talairach coordinates were inputted into Talairach Client software (version 2.4.3; Lancaster et al., n.d.), and the regions were recorded.

2.7 Statistical analysis

All statistical analyses were run using SPSS software (version 25.0; IBM Corporation, Armonk, NY, USA). Demographics and clinical characteristics were assessed using descriptive

and frequency statistics in SPSS. Information on these characteristics were collected from questionnaires completed at the first visit.

To determine the differences in accuracy and reaction between the 0-back and 2-back conditions, two-tailed paired sample t-tests were run with a significance level of $p < .05$. These data were obtained from output from E-Prime as a result of the task being run. For accuracy, the E-Prime file provided correct answer and the answer that the participant provided, which were summed to determine the overall accuracy for each participant for the entire task. In trials that were not answered, they were included as incorrect. For the reaction time, the E-Prime file provided the total reaction time (in ms) for the 0-back and 2-back conditions. Reaction times included only correctly answered trials and were created directly through the E-Prime output file.

Two-tailed Spearman correlations ($p < .05$) were run to quantify the relationship between task performance (i.e., accuracy) and MADRS score to determine if illness severity could be indicative of performance between the two conditions. Separate correlations were run for the 0-back and 2-back conditions.

Finally, correlations were conducted to determine if there was any relationship between performance accuracy, neural activity, and MADRS score across the two conditions. First, regions of interest (ROIs) were created using the MarsBaR toolbox (http://marsbar.sourceforge.net/) in MatLab. Using the significant areas found in the second level imaging analysis, ROIs were created for each condition. From here, second level contrast files for each condition (i.e., 0-back > 2-back and 2-back > 0-back) were used to extract the ROI data for all ROIs in each participant. Once these data were extracted, results were estimated, saved, and loaded into the MatLab console for analysis. Beta weights from each participant from each ROI and condition were then correlated using two-tailed Spearman correlations ($p < .05$) against the participants' corresponding

performance accuracy (for each condition) and MADRS scores to determine if there were any relationships present.

CHAPTER 3: RESULTS

3.1 Demographics

A total of 29 participants (male = 5, female = 24; mean age = 37.6 ± 14.3 years) were recruited from August 1, 2017 to February 28, 2019. There was one additional participant who was scanned during this timeframe but had to be excluded from this analysis due to incidental findings during the scan.

The majority of the present participants were right-handed (n = 25, 86.2%), white (n = 25, 86.2%), between the ages of 18-29 years (n = 13, 44.8%), never married (n = 19, 65.5%), had completed at minimum an associate's degree (n = 19, 65.5%), were currently employed or a student (n = 10, 34.5% and n = 5, 17.2%, respectively), and were treated with pharmacotherapy (n = 22, 83.4%; 47.6% of the total sample being prescribed either an SSRI or SNRI). A more in-depth description of the demographic data is presented in Table 1.

Table 1

Demographics of Participants (n = 29)

	n (%)
Gender	
Female	24 (82.8)
Male	5 (17.2)
Age (years)	
18-29	13 (44.8)
30-39	3 (10.3)
40-49	5 (17.2)
50-59	7 (24.1)
60+	1 (3.4)
Handedness	
Left	4 (13.8)
Right	25 (86.2)
Race/Ethnicity	
South Asian	1 (3.4)
White	25 (86.2)
Arab	1 (3.4)
Black	1 (3.4)
East Asian	1 (3.4)
Marital status	
Never married	19 (65.5)
Married	8 (27.6)
Separated	2 (6.9)
Highest education	
Grade 11	1 (3.4)
Grade 12, no diploma	1 (3.4)
High school diploma	2 (6.9)
Some college	6 (20.7)
College (occupational/technical/vocational program)	4 (13.8)
College (academic program)	4 (13.8)
Bachelor's degree	5 (17.2)
Master's degree	5 (17.2)
Doctoral degree	1 (3.4)
Employment status	
Currently employed	10 (34.5)
Disabled, temporarily or permanently	4 (13.8)
Unemployed	1 (3.4)
Student	5 (17.2)
Retired	3 (10.3)
Other	6 (20.7)

Household income (per year)	
Less than $10,000	3 (10.3)
$10,000 – $24,999	7 (24.1)
$25,000 – $49,999	4 (13.8)
$50,000 – $74,999	3 (10.3)
$75,000 – $99,999	1 (3.4)
$100,000 – $149,999	5 (17.2)
$150,000 – $199,999	4 (13.8)
$200,000 or more	1 (3.4)
Unsure	1 (3.4)
Medication	
SSRIs (citalopram, escitalopram, fluoxetine, paroxetine, sertraline)	15 (35.7)
SNRIs (duloxetine, venlafaxine)	5 (11.9)
Tricyclics (amitriptyline, doxepin)	2 (4.76)
Benzodiazepines (clobazam, clonazepam, lorazepam, temazepam)	5 (11.9)
Other (bupropion, lithium, methylphenidate, trazodone, zopiclone)	8 (19.04)
None	7 (16.6)

Abbreviations: SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors.

3.2 Clinical characteristics

Participants demonstrated an average score of 20.41 ± 10.78 on the MADRS, which is indicative of moderate MDD symptoms. Approximately 58.6% (n = 17) had a MADRS score higher than 21; moreover, 10.33% of these participants (n = 3) demonstrated a MADRS score that was consistent with severe depressive symptoms (score over 35). See Table 2 for a breakdown of MADRS scores. Importantly, while only 58.6% of participants had a MADRS score consistent with moderately severe symptoms at their baseline visit, this was due to the time lapse between their screening and baseline assessments. All participants at their screening visit were required to have a MADRS score over 20 points; however, as demonstrated, this may have improved between these two visits, leading to the decreased symptomology at baseline.

Next, participants displayed an average performance on all domains on CNSVS, as standardized scores are considered average when they are between 90-108. Notably, in the neurocognitive score, 13.8% (n = 4) of participants performed below average (i.e., below a standard score of 90), whereas 24.1% (n = 7) performed above. Additionally, in the composite score, only 6.9% (n = 2) fell below the average score, whereas 41.4% (n = 12) were above. This indicates that, based on the performance on this test, participants were not blatantly cognitively impaired compared to the population average. See Table 3 for a breakdown of the performance on the domains of CNSVS.

Table 2

Total MADRS Scores

Total MADRS Score	n (%)
0-10	7 (24.1)
11-15	1 (3.44)
16-20	4 (13.8)
21-25	6 (20.7)
26-30	7 (24.1)
31-35	1 (3.44)
36-40	2 (6.89)
40+	1 (3.44)

Abbreviations: MADRS = Montgomery-Åsberg Depression Rating Scale.

Table 3

Mean CNSVS Domain Scores

Domain	Mean (± SD)
Verbal memory	105.48 (± 13.90)
Visual memory	102.52 (± 16.81)
Psychomotor	100.83 (± 24.42)
Reaction time	101.48 (± 13.38)
Attention	94.83 (± 22.79)
Cognitive flexibility	101.59 (± 21.59)
Processing speed	102.38 (± 16.57)
Executive function	102.38 (± 20.85)
Composite	104.69 (± 14.79)
Neurocognition	99.97 (± 11.08)

3.3 N-back performance

For the n-back task, the overall correct number of answers was 56.9 (out of a possible total of 80; 71.0%); for the 0-back and 2-back conditions, the average number of correct answers were 30.1 (75.2%; SD = 9.63) and 27 (67.5%; SD = 8.78), respectively (see Table 2). The difference in accuracy between the 0-back and 2-back conditions was found to be significant, with participants typically performing better at the 0-back level ($t(28) = 2.61$, $p = .013$).

Table 4

Number of Correct Scores on N-back (Total vs. 0-back vs. 2-back)

	Mean (% correct)	Standard deviation	Minimum	Maximum
N-back total score	56.86 (71.1)	17.46	11	78
0-back score	30.07 (75.2)	9.63	5	40
2-back score	27 (67.5)	8.78	6	39

For reaction time, participants were significantly faster at correctly responding in the 0-back (mean: 840.76 ms) condition than the 2-back (mean: 1005.61 ms; $t(28) = -5.127$, $p = .001$), therefore indicating that participants, on average, performed quicker and better at the 0-back level than the 2-back.

In correlations between MADRS scores and accuracy on the 0-back and 2-back conditions, neither was found to be significant (0-back: $r = .248$, $n = 29$, $p = .194$; 2-back: $r = .310$, $n = 29$, $p = .102$), indicating that illness severity was not associated with performance on either level of the n-back task. Notably, while these did not return significant p values (possibly due to the sample size), the Spearman correlation coefficients offered a medium sized effect.

3.4 Imaging analysis

3.4.1 Neural correlates of 0-back > 2-back

Observing the 0-back condition, after removing activity at the 2-back level, significant voxel clusters were only retained when the data was uncorrected. Significant voxel clusters included the bilateral insular cortex/Brodmann area (BA) 13 ($p_{uncorr} < .01$) and the middle occipital gyrus (MOG; $p_{uncorr} < .05$; see Table 5, Figure 2).

Table 5

Significantly Activated Voxel Clusters for 0-back > 2-back

Talairach region	Talairach coordinates (x y z)	MNI coordinates (x y z)	$p_{FWE-CORR}$	p_{uncorr}	Minimum voxel cluster extent (K_E)	t-value at peak
Right insula	54 -22 16	54 -22 14	.015	.002	1173	4.82
BA 13, left insula	-52 -31 19	-54 -32 18	.001	< .001	2291	4.81
Middle occipital gyrus	45 -95 3	44 -98 -2	.171	.031	521	4.78

Note: $p_{FWE-CORR} < .05$; $p_{uncorr} < .001$.
Abbreviations: MNI = Montreal Neurological Institute; BA = Brodmann area.

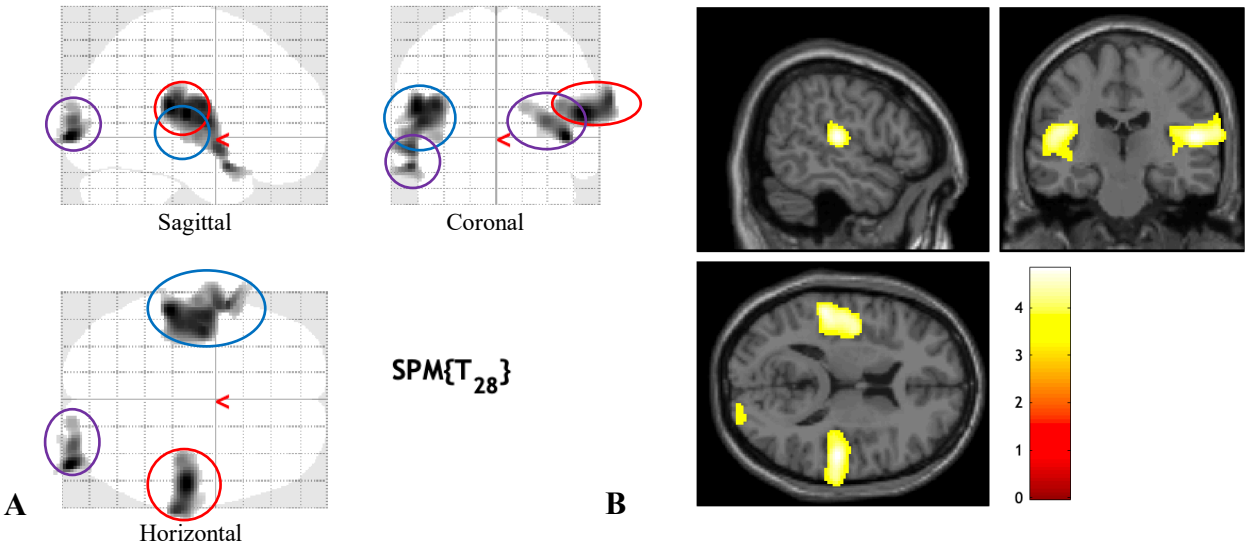

Figure 2. Activity during the 0-back condition exclusively. These are images that are created based on the averaged activity for the entire group (e.g., second level analysis). The activity is laid over a glass brain image provided by SPM12 (Figure 2A) and a standard T1-weighted canonical anatomical scan (Figure 2B) that is also provided by SPM12. Red arrows are placed at the [0,0,0] location of the grid and is movable throughout the glass brain image. (A) is a glass brain view of the regions that were significantly activated during the 0-back condition after removing those that were also present in the 2-back condition. The red circle corresponds to the right insula [MNI coordinates: 54 -22 14]. The blue circle corresponds to the left insula (Brodmann area 13) [-54 -32 18]. Finally, the purple circle corresponds to the middle occipital gyrus [44 -98 -2]. Additionally, under each glass brain image, the planes by which the images are created are denoted. (B) offers an alternate view of significant clusters on a T1-weighted scan with t-value ranges in the legend.

3.4.2 Neural correlates of 2-back > 0-back

After subtracting activity during the 0-back condition from the activity during the 2-back condition, there were several clusters of significant voxels that were returned after correction (FWE). There were three regions that showed significant activation during the 2-back condition: the middle frontal gyrus (right BA 9 and bilateral BA 10; $p_{FWE\text{-}CORR} < .05$), the medial frontal gyrus (right BA 6; $p_{FWE\text{-}CORR} < .001$), and the inferior parietal lobule (bilateral BA 40; $p_{FWE\text{-}CORR} < .05$; see Table 4, Figure 3).

Table 6

Significantly Activated Voxel Clusters for 2-back > 0-back

Talairach region	Talairach coordinates (x y z)	MNI coordinates (x y z)	$p_{FWE\text{-}CORR}$	$q_{FDR\text{-}CORR}$	Minimum voxel cluster extent (K_E)	t-value at peak
Right BA 10, middle frontal gyrus	31 47 17	32 48 18	< .001	.001	424	7.77
Right BA 6, medial frontal gyrus	7 28 35	8 28 38	< .001	.001	366	7.37
Right BA 40, inferior parietal lobule	47 -51 -32	46 -48 42	< .001	.017	171	6.69
Left BA 9, middle frontal gyrus	-47 24 34	-48 24 36	.003	.089	78	6.40
Left BA 40, inferior parietal lobule	-50 -40 40	-50 -42 42	.030	.600	6	5.99
Left BA 10, middle frontal gyrus	-36 46 11	-36 48 12	.015	.344	23	5.95

Note: $p_{FWE\text{-}CORR} < .05$.
Abbreviations: MNI = Montreal Neurological Institute; BA = Brodmann area.

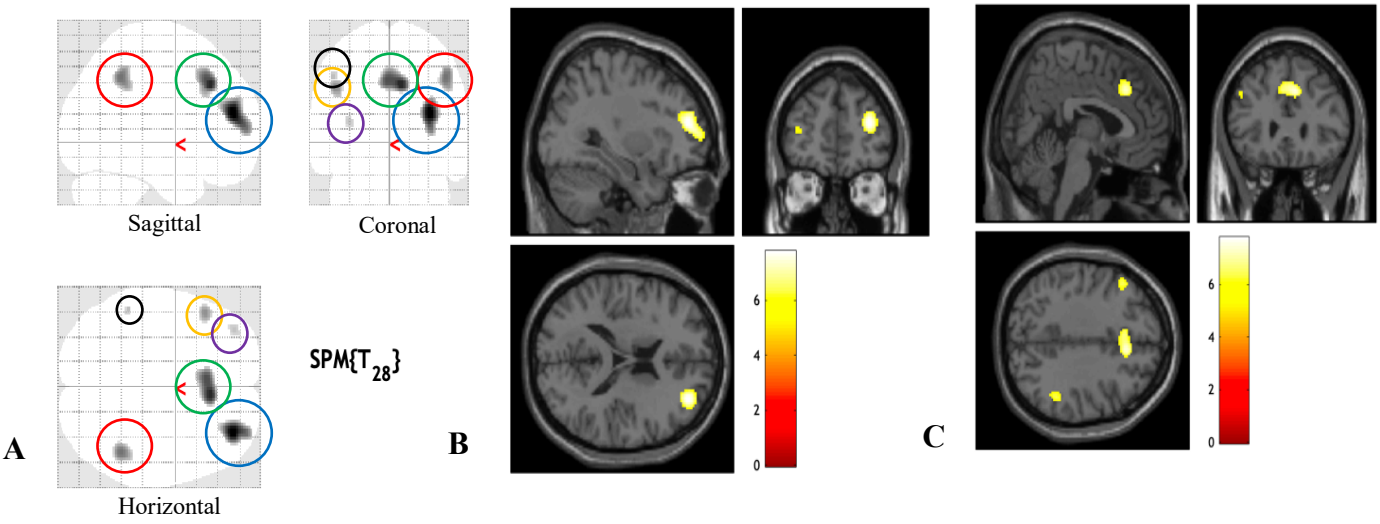

Figure 3. Activity during the 2-back condition exclusively. These are images that are created based on the averaged activity for the entire group (e.g., second level analysis). The activity is laid over a glass brain image provided by SPM12 (Figure 3A) and a standard T1-weighted canonical anatomical scan (Figures 3B-C) that is also provided by SPM12. (A) is a glass brain view of the regions that were significantly activated during the 2-back condition after removing those that were also present in the 0-back condition. Red arrows are placed at the [0,0,0] location of the grid and is movable throughout the glass brain image. The red circle corresponds to the right Brodmann area (BA) 40/inferior parietal lobule [MNI coordinates: 32 48 18]. The blue circle corresponds to the right BA 10/middle frontal gyrus [8 28 38]. The green circle corresponds to the right BA 6/medial frontal gyrus [46 -48 42]. The light orange circle corresponds to the left BA 9/middle frontal gyrus [-48 24 36]. The black circle corresponds to the left BA 40/inferior parietal lobule [-50 -42 42]. Finally, the purple circle corresponds to the left BA 10/medial frontal gyrus [-36 48 12]. Additionally, under each glass brain image, the planes by which the images are created are denoted. It is notable to mention that in Figures 3B and 3C that these are the same and remain constant. (B) offers an alternate view of significant clusters on a T1-weighted scan with t-value ranges in the legend. (C) also offers significant clusters on a T1-weighted scan but is from a more internal view.

3.5 Clinical characteristics, n-back performance, and functional data

3.5.1 MADRS and functional activity

Upon correlation of the MADRS data with functional activity in the ROIs returned at the 0-back (bilateral insula and middle occipital gyrus) and 2-back levels (middle and medial frontal gyri and inferior parietal lobule), no statistically significant relationships were found (see Table 7). Notably, although these were not statistically significant, the effects of some of these correlations was substantial. In the left insula at the 0-back level, the Spearman correlation coefficient was .273, indicating a moderate correlation. Additionally, in the 2-back level, a small, negative correlation was found with the medial frontal gyrus, and a small, positive correlation was found with the right inferior parietal lobule.

Table 7

MADRS Scores Correlated with ROIs Discovered in 0-back and 2-back Conditions

	Spearman correlation coefficient (r)	P value
0-back		
Left insula	.273*	.152
Middle occipital gyrus	-.115	.552
Right insula	.040	.838
2-back		
Left BA 10	-.002	.990
Left inferior parietal lobule	.025	.896
Left middle frontal gyrus	-.069	.721
Medial frontal gyrus	-.043	.826
Right middle frontal gyrus	.066	.732
Right inferior parietal lobule	.176*	.360

Notes: * indicates small effect size.
Abbreviations: BA: Brodmann area; MADRS: Montgomery-Åsberg Depression Rating Scale; ROIs: regions of interest.

3.5.2 Performance accuracy and functional activity

Furthermore, in correlations between performance accuracy and functional activity between the two conditions in the ROIs determined in the second level analysis, all relationships were significant at the 2-back condition (see Table 8). Notably, while these correlations were statistically significant, a large portion of the Spearman correlation coefficients, in both the 0-back and 2-back conditions, were small to medium.

Table 8

Accuracy Correlated with ROIs Discovered in 0-back and 2-back Conditions

		Spearman correlation coefficient (r)	P value
0-back			
	Left insula	.249*	.194
	Middle occipital gyrus	.061	.753
	Right insula	.225*	.241
2-back			
	Left BA 10	.436**	**.018**
	Left inferior parietal lobule	.399**	**.032**
	Left middle frontal gyrus	.367**	**.050**
	Medial frontal gyrus	.390**	**.037**
	Right middle frontal gyrus	.402**	**.031**
	Right inferior parietal lobule	.461**	**.012**

Notes: * indicates small effect size; ** indicates medium effect size. Bold indicates significance at $p < .05$.
Abbreviations: BA: Brodmann area.

CHAPTER 4: DISCUSSION

Overall, the present study found the following. First, participants demonstrated an average MADRS score of 20.41, suggesting moderately severe depressive symptoms. Additionally, their performance on CNSVS was consistent with the average of the general population, suggesting no cognitive impairment compared to HC. On the n-back task, participants demonstrated a significantly decreased accuracy and increased reaction time at the 2-back level than the 0-back level. Next, in correlations between MADRS score and accuracy, there did not appear to be a relationship between these two variables in the present participants. In the 0-back condition, regions associated with rest and attention were significantly activated, whereas during 2-back, areas of activity were primarily regions associated with complex cognitive processes. In correlations of MADRS, performance accuracy, and n-back activity, symptom severity was not found to be associated with activity in either the 0-back or 2-back conditions. Interestingly, performance accuracy was not found to be related to activity in the 0-back condition, but participants that achieved higher accuracy in the 2-back condition demonstrated higher levels of activity in the observed regions.

4.1 Clinical characteristics

One of the most notable findings in the clinical data was that on CNSVS, a well-documented and standardized test of neurocognition, participants had an overall average score that was consistent with typical functioning. This result may suggest that in the present participants, difficulties during the n-back may have been due to MDD symptoms or other, unobserved qualities, rather than substantial and quantifiable cognitive deficits.

Importantly, while participants demonstrated cognitive abilities that did not differ from the general population, this is not to say that these participants were not cognitively impaired. While

CNSVS is a great tool for capturing a basic snapshot of cognition, one single timepoint measurement on this assessment is not indicative of overall cognitive function or decline. In MDD patients, cognitive decline is typically related to previous functioning, rather than deficits from the general population. Studies have found a relationship between premorbid intelligence quotient (IQ) and cognition in MDD, in that patients with MDD demonstrate a notable decrease in cognitive function based on premorbid and current IQ (Lager, Melin, Hemmingsson, & Sörberg Wallin, 2017). Therefore, this indicates that while the present participants demonstrated typical cognitive functioning compared to the general population, they may still have been substantially impaired based on previous functioning.

4.2 N-back performance

As described in Chapter 1.5.2, as the n-task becomes more difficult (i.e., increasing cognitive load from 0-back to 2-back), it is common for participants to demonstrate decreases in accuracy and increases in reaction time, indicating they were performing slower and worse on the task as it grew harder (Bartova et al., 2015). This was seen in the present participants; they required more time to think about the correct answer during the 2-back condition and were less accurate than in the 0-back condition.

However, in comparison to HC from other studies of 0- and 2-back conditions, the present participants performed worse on the n-back task. In a 2015 study by Bartova et al., HC were 98% and 81% correct on the 0-back and 2-back conditions, which is substantially higher than our participants (compared to 75% and 67%, respectively). Additionally, our participants were much slower than HC in this study, as they demonstrated 561 ms and 476 ms reaction times for the 0-back and 2-back conditions, compared to 840 ms and 1005 ms, respectively (Bartova et al., 2015).

This suggests that MDD participants, while conforming to the trends of HC in terms of cognitive load, overall demonstrate a much poorer performance on the n-back task.

In the comparison of MADRS data and accuracy at the 0- and 2-back levels, neither correlation was found to be significant, indicating that in this sample, MADRS score did not have a significant association with performance on either the 0-back or 2-back task. Notably, as earlier described, while these were not statistically significant, the correlation coefficients are considered to be at the mid-level; however, by including more participants, this may demonstrate that these effects were exaggerated, leading to an inflated correlation coefficient. Including more participants will offer clearer and more generalizable findings into the association demonstrated here.

4.3 Neural correlates of 0-back

The 0-back condition is often regarded as the control condition for the task, as it requires very little WM input and more so employs a recognition type recall; with a larger ‘n’, more maintenance and updating is required (Richards, Berninger, Winn, Lee Swanson, & Patricia Stock, 2009). In this condition, the regions that had the largest and most significant voxel clusters were the bilateral insular cortex and the MOG, which are found to be functionally connected to the default mode network (DMN) through the salience network and have crucial functions in visual input, respectively (Hu et al., 2019; Iwabuchi et al., 2014).

The insular cortex (insula) is found deep within the brain and is stated to have functions imperative to cognition, such as the processing of incoming stimuli, attention, emotion, and conscious thought (Cauda et al., 2011; Chang, Yarkoni, Khaw, & Sanfey, 2013). Studies have suggested that patients with MDD display significantly increased activity in this region compared to HC, suggesting its “overworking” (i.e., they require more cognitive resources to conduct tasks than HC) (Iwabuchi et al., 2014). In conjunction with results from other studies that corroborate

this overwork in depressed participants, it is clear that overall, patients with MDD require more resources to participate in cognitively demanding tasks (Harvey et al., 2005; Iwabuchi et al., 2014).

Moreover, the insula has been noted to be connected to the DMN due to its role in the salience network; it works as a bridge between the DMN and the rest of the brain and aids in the movement from this network to other cognitive networks (Iwabuchi et al., 2014; Sawaya et al., 2015). The main role of the salience network, and specifically the insula, is to help to discern novel (or salient) stimuli from those that are not (Bonnelle et al., 2012; Manoliu et al., 2014). Additionally, the DMN is a group of structures that are involved in resting state activities and is employed during activities such as passive rest, mind wandering, and self-directed thought (Sawaya et al., 2015). In assessments of HC, significant suppression of the DMN has been found in tasks that require attention, thereby allowing participants to focus on the task and decreasing mind wandering and rest (Bartova et al., 2015).

Conversely, in participants with MDD, a reduced suppression of the DMN has been routinely noted; this has been reported to be linked to diagnosis-specific symptoms (Bartova et al., 2015). It has also been found that as severity of illness increases, suppression of the DMN is further reduced (Grimm et al., 2009). Other research has cited that the insula itself is also suppressed in attention-based tasks, further solidifying its relationship with the DMN (Sliz & Hayley, 2012).

Next, the MOG, as suggested by its name, is a portion of the occipital lobe, which has many implications in the processing of visual stimuli; the MOG has important roles in this visual network as a result (Hu et al., 2019). Therefore, in a task requiring the processing and interpretation of incoming visual stimuli, it is understandable that participants would demonstrate activity in this region.

4.4 Neural correlates of 2-back

In the 2-back condition, after removing activity from the 0-back condition, the remaining regions of significantly activated activity were the medial frontal gyrus (BA 6), the inferior parietal lobule (BA 40), and the middle frontal gyrus (BA 9/10).

The medial frontal gyrus is a large gyrus found in the frontal lobe of the human brain that houses the smaller and more specific BA 6. BA 6 is a relatively understudied structure, but is activated in motor control; however, rostral portions have been found to be important in higher order executive functions and cognition, likely due to their proximity to the frontal lobe (Hanakawa et al., 2002; Tanaka, Honda, & Sadato, 2005). In the present study, at the 2-back level, participants were required to elicit more neural resources in the execution of the task. Research has suggested that BA 6 is imperative in cognitive processes, especially tasks that require more resources and has been found to be significantly activated in n-back research in MDD patients (Schöning et al., 2009).

The inferior parietal lobule is part of the larger parietal lobe, which contains the majority of visual processing structures, and research suggests that it may also be involved in visual WM as a result (Berryhill & Olson, 2008; Townsend, Bookheimer, Foland–Ross, Sugar, & Altshuler, 2010). In the meta-analysis by Owen et al. (2005), they found that HC demonstrated significant activity in this region during the n-back task, which was then further corroborated to be further increased in MDD patients (Schöning et al., 2009). As this region has been largely implicated in the visual WM of both HC and MDD patients, it is unsurprising that it would be apparent in this sample of MDD participants. In demonstrating this, the present results add to the body of research that has already been confirmed in this population.

Finally, significantly increased activation was found in the middle frontal gyrus, or BA 9/10. This region is also considered to be part of the PFC, though its exact location varies (e.g.,

rostral, anterior, rostrolateral) across studies and their modalities (Dumontheil, Burgess, & Blakemore, 2008; Peng, Steele, Becerra, & Borsook, 2018; Reynolds, West, & Braver, 2009). Recently, this small region has garnered a lot of attention due to the understanding that it is important in the higher-order processing of pain, attention, and memory (Dumontheil et al., 2008; Peng et al., 2018; Reynolds et al., 2009). BA 9/10 is found to be important in the integration of complex cognitive processes, including WM, especially at an increased cognitive load (Burgess, Gilbert, & Dumontheil, 2007). Research has found that activity in other portions of the PFC (e.g., dorsolateral), the ACC, and the parietal cortex are correlated with activity in BA 9/10, further suggesting its importance in WM tasks such as n-back, as well as MDD (Gilbert, Gonen-Yaacovi, Benoit, Volle, & Burgess, 2010).

4.5 MADRS scores and functional imaging data

As described, none of the correlations between either cognitive load (i.e., 0-back or 2-back) were found to be statistically significant. As previously described, as these were mid-sized effects, at a larger sample size, this may alter the association and offer different insight into the relationship between these two variables. First, a small correlation coefficient was observed in the 0-back condition with the left insula. As discussed earlier, the insula is part of the salience network and is connected to the DMN as a result (Bartova et al., 2015; Grimm et al., 2009; Manoliu et al., 2014). The DMN is found to be suppressed during tasks requiring attention; however, in MDD patients, research has found a reduced suppression as severity of illness increases (Bartova et al., 2015; Grimm et al., 2009). Our present participants demonstrated a mean MADRS score of approximately 20, which is consistent with moderate symptoms, and offering further explanation to the results seen.

Next, small effect sizes were seen at the 2-back level in the medial frontal gyrus and right inferior parietal lobule. Interestingly, the correlation demonstrated with the medial frontal gyrus was negative, insinuating a small inverse relationship. This correlation suggests that participants with a higher MADRS score demonstrated a lesser degree of activation, whereas those with lower MADRS scores demonstrated higher levels of activity. fMRI research in MDD patients that involves this region is fairly scarce; however, this finding suggests that it may be more difficult with patients with more severe symptoms to engage all required neural networks to complete more cognitively demanding tasks. Finally, there was a small and positive correlation between the right inferior parietal lobule and MADRS scores, indicating that as MADRS scores increased, participants required more resources from this region to complete the task.

4.6 Performance accuracy and functional imaging data

As discussed, as the task became harder (i.e., as it increased from 0-back to 2-back), participants demonstrated a notable decrease in accuracy, which is also consistent with the literature for HC. In the 0-back condition, while none of the correlations were statistically significant, there were small effects demonstrated within the activity seen in the bilateral insula. Although participants performed fairly well on this portion of the task (75.2% accuracy), this correlation demonstrates that participants who had higher scores displayed greater activity in this region, suggesting that better performing participants may have required more resources and were working harder (i.e., as the insula is involved in determining salient from non-salient stimuli) to achieve their higher accuracy.

In the 2-back condition, all correlations were mid-sized and statistically significant. Overall, this finding also suggests that participants who were more accurate in completing the task required more resources in regions implicated in complex cognitive processes. Importantly, the

cognitive effort hypothesis suggests that cognitively demanding tasks are more difficult for MDD patients, as they are overall less likely to want to use neural resources on these unappealing tasks (Bowie et al., 2017). This is seen here, as participants who achieved a higher degree of accuracy may have felt better about their performance, allowing them to allocate more resources to complete the task, leading to a significant correlation between performance and activity.

4.7 Limitations and future directions

One of the most notable limitations is the modest sample size (n = 29). With a fairly small n, this decreases power, thereby limiting the conclusions that can be drawn about MDD patients as a whole. While the current sample did demonstrate some notable results, many of the correlations were massively underpowered and were statistically insignificant as a result. A power analysis would have been beneficial in this situation to determine the minimum number of participants required to achieve sufficient statistical power. As described, due to the low sample size, this may have incorrectly inflated or aided in the misinterpretation of correlational analyses, further demonstrating the necessity of a larger sample. Additionally, there was no controlling for age, length or recurrence of illness, years of education, or medication, which may have caused some participants to have a more pronounced deficit or advantage in the WM task. There was also a disproportionate ratio of men to women; the sample was made up of 83% women, which may have led to gender dependent differences that are not as representative of the entire population.

Moreover, as there were no HC in the present study, and the remaining CAN-BIND studies do not use the n-back task, it was difficult to draw conclusions of what would be considered abnormal activation (i.e., increased or decreased, compared to a healthy condition). With a healthy group of age-matched participants, this would allow for the comparison between activity at each

level. While making observational analyses without a control group are still effective, it cannot fully describe the entire scenario, as there is not a "normal" condition to compare to.

In the n-back task, it may be beneficial to include a 1-back condition, rather than exclusively a 0-back and 2-back. The 0-back condition is often seen as a control condition; as a result, the conclusion that the aforementioned regions are significantly activated as cognitive load decreases may not be entirely accurate. By incorporating a 1-back condition, this would likely decrease the activity in the DMN, thereby making regions that are significantly activated as 'n' increases to be more clearly visualized. Alternatively, it would also be interesting to see what differences there are in activity between a resting state scan (i.e., when participants are not engaging in a task) compared to when participants are doing the 0-back condition, to determine which regions are activated exclusively as part of the n-back task.

Next, further investigation into the two levels of the n-back task may be advantageous to further understand the mechanisms at work. Functional connectivity analyses may be interesting to pursue to have a better idea of what other regions may be affected at the 0-back and 2-back conditions, specifically in MDD patients.

Including additional and more specific (e.g., assessing the different components of WM) WM measures, such as complex span tasks that have been found to assess higher-level cognition (i.e., reasoning), or the Sternberg task (Jesulola et al., 2018; Rottschy et al., 2012). This also may be a preferable to the n-back task, as some studies have suggested that this is not an accurate or realistic gauge of WM (Miller, Price, Okun, Montijo, & Bowers, 2009). A 2007 study by Kane et al. found that the n-back task is not entirely representative of WM function and that it may be better equipped to demonstrate general intelligence. They determined that n-back task performance cannot be generalized to other WM assessments, especially as they primarily assess recognition,

rather than recall (Kane, Conway, Miura, & Colflesh, 2007). Therefore, it would be beneficial to further correlate performance on the n-back task in this sample with other assessments of WM.

4.8 Conclusions

The present study worked to elucidate the neural correlates of WM in patients with MDD during the n-back task at 0- and 2-back, while also considering clinical characteristics, such as MADRS. Our participants demonstrated noticeable and profound difficulties in during the n-back task; however, performance on CNSVS did not corroborate significant cognitive deficits in this sample; however, this may not be representative of the participants' true cognitive decline from their previous functioning. Additionally, as cognitive load increased, participants were seen to perform significantly worse on the task, which is found regardless of diagnosis; although, our participants were found to do substantially worse in terms of accuracy and speed on the n-back task compared to literature including HC (Bartova et al., 2015).

It was hypothesized that as cognitive load increased, participants would perform worse on the n-back task, which was confirmed and is thought to be because of the cognitive effort hypothesis (Bowie et al., 2017). In consideration of this, it is suggested that participants did not perform as well as HC because of the amount of effort required to complete the task, which is corroborated in the correlations of task performance and activity at both levels. Particularly in the 2-back condition, significant correlations were seen in almost all regions associated with the 2-back condition, which further supports the notion that MDD participants require more cognitive effort to perform a task as well as a HC.

These findings add to the existing literature on the cognitive difficulties seen in MDD patients. While these participants did not display any substantial cognitive deficits on standardized tests of neurocognition (i.e., CNSVS), they did demonstrate a significantly affected n-back

performance, which was found to be unrelated to MADRS score or symptom severity. Notably, performance was significantly correlated with activity in regions implicated in MDD and WM during the more cognitively difficult 2-back task, which requires further development going forward.

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